REMARKS

Claims 1, 7, 20, 25, 29-30, 33, 35, and 43-46 are pending in the subject application. By this Amendment, Claims 1 and 35 have been amended. Support for the claim amendments can be found at least in the previous version of the claims. Applicants maintain that the amendments to the claims do not raise an issue of new matter. Entry of the amendments is respectfully requested.

Objection to Claim 29

Applicants note the Examiner's objection to Claim 29 as being a substantial duplicate of Claim 35. Upon a finding that both claims are otherwise allowable, applicants agree to cancel Claim 29.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1, 7, 20, 25, 29-30, 33, 35, and 43-46 are rejected as failing to comply with the enablement requirement. The Examiner alleged that the application does not contain an enabling description of the plasmid recited in the claims. The description of the plasmid in the claims has now been simplified. The application on page 22 indicates that the plasmid was made by inserting the smooth muscle alpha actin (SMAA) promoter into an EYFP vector available from Clontech to produce pSMAA/EYFP. In SMAA/EYFP, the EYPF gene was removed and *hSlo* was inserted in its place to give plasmid SMAA/*hSlo*. The nucleotide sequence of *hSlo* is available at Genbank Accession No. U23767 [paragraph [0061], page 22 of application]. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1, 7, 20, 25, 29-30, 33, 35, and 43-46 are rejected as vague and indefinite because the Examiner alleged that the metes and bounds of the term "derived from" in Claims 1 and 35 is not clear. The claims have been amended to no longer recite the term "derived from" thereby obviating this rejection.

Rejections under 35 U.S.C. §103(a)

Claims 1, 7, 20, 25, 29-30, 33, 35, and 43-46 are rejected as being unpatentable over Geliebter et al. (U.S. Patent No. 6,150,338) in view of Leiden et al. (U.S. Patent No. 6,436,907) and evidenced by Foster et al. (J. Biol. Chem. 256: 11995-12003) and Melman et al. (Gene Therapy 15: 364-370, 2008).

Applicants respectfully traverse this rejection.

Applicants note that previous inventions were based on the supposition that the major effect of maxi-K gene transfer was mediated at the level of the corporal smooth muscle cell, and as the Examiner states, this was duly noted in the specifications of the prior patent (U.S. Patent No. 6,150,338). However, it is important to point out that all of the work from which these conclusions were drawn were obtained with the CMV promoter, which is well known to be nonselective, and therefore, could result in expression of the maxi-K channel in multiple cells types upon injection into the penis, for example, arterial (vascular), corporal (specialized vascular), neural, interstitial (in humans; Shafik et al., Arch. Andrology 52: 255-262, 2006; Shafik, J. Sex. Med. 4:66-71, 2007; copies attached hereto) and endothelial cells. This lack of transfection specificity means that each of these other cell types could contribute to the enhanced erectile capacity observed following penile injection of CMV promoter coupled to the Maxi-K channel, especially the endothelial cell which is critical to penile erection (via release of

nitric oxide (NO)), and the activity of the endothelial cell would also be enhanced via over-expression of the Maxi-K channel. As such, while the data are consistent with smooth muscle cells providing the primary mode of action for the enhanced erectile capacity observed with the CMV promoter, the data cannot exclude the possibility that multiple cell types (especially the endothelial cells) within the penis may also contribute to this response.

By analogy, applicants maintain that there are examples in the pharmaceutical industry where it was generally observed that development of second generation drugs with more specificity than their first generation counterparts (based on the presumptive primary mode of action- that is, an effect mediated by a particular receptor subtype) were generally less effective than their less selective predecessors. That is, the "dirty" drugs (i.e., drugs with multiple receptor mediated actions or off-target effects) were frequently more efficacious than the more selective second generation drugs. In addition, it is well documented that intracavernous pharmacotherapy for erectile dysfunction is enhanced by including more drugs that affect distinct targets and/or cell types within the penis. When viewed from this general physiological/pharmacological perspective, it would not be obvious that a more selective expression pattern of the Maxi-K channel would lead to enhanced erectile function/capacity. Nonetheless, applicants conducted the experiments with the SMAA promoter to further probe the primary mode of action of the original product (i.e., CMV promoter).

To be clear, applicants would like to point out that applicants utilized the SMAA promoter BECAUSE it was known to be smooth muscle specific, in order to more directly evaluate the contribution of corporal smooth muscle to enhance erectile capacity/function. The fact that Leiden et al., and others, had already shown that SMAA had a vascular smooth muscle specific expression pattern, therefore, has no impact on the

following three independent lines of investigation that are not obvious: 1) that pSMAA-*hSlo* would in fact produce greater levels of *hSlo* expression *in situ* (from a nominally smaller number of transfected cells), 2) that use of pSMAA-*hSlo* would result in improved erectile responses to low levels of nerve stimulation in rats (in fact, this observation actually implies that patients with erectile dysfunction of neurogenic origin might be more responsive to pSMAA- thereby expanding the potentially responsive patient cohort- this might also indicate that the CMV promoter was in fact suppressing nerve mediated conduction at some level; thus, inhibiting the impact of *hSlo* transfection at lower levels, but not submaximal levels of neural stimulation/activation), nor was it obvious, 3) that use of pSMAA-*hSlo* could improve erectile function and behavior in nonhuman primates with atherosclerosis-related erectile dysfunction. That is, it would not be obvious that transfection of ONLY the corporal smooth cells would restore erectile function and sexual behavior in a disease that is known to have major impact on the endothelial cell function (i.e., altered flow mediated dilation) as well as vascular structure/function (i.e., the presence of necrosis, inflammation and calcification resulting in diminished vessel function) (see below for a more detailed description). In this scenario, and based on common knowledge in the field at the time, the corporal smooth muscle cell- the presumptive primary target of the Maxi-K channel gene transfer- would only be effective in the presence of atherosclerosis if the vasculature subserving the penis is able to dilate (to increase blood flow to the penis), and furthermore, if the endothelial cell network can release sufficient amounts of the corresponding signals required for vascular and corporal smooth muscle relaxation and penile erection. Both of these processes are compromised by atherosclerosis. As such, it would not be obvious that the SMAA promoter would be effective- especially if, as noted above, the endothelial cells were a target for the Maxi-K channel (i.e., when using CMV promoter), where increased hyperpolarization is linked to

increased NO release (due to increased intracellular calcium levels resulting from the enhanced hyperpolarization of the endothelial cells).

As previously noted, the paper by Christ et al. (2008) documented dramatic improvements in erectile function and sexual behavior following treatment with pSMAA-*hSlo* in cynomologous monkeys with erectile dysfunction secondary to diet-induced atherosclerosis. Applicants would like to further comment on the importance of this particular study to the non-obviousness of the use of the SMAA promoter. In this regard, the majority of patients with erectile dysfunction have a vascular component, and atherosclerosis is a well documented risk factor for erectile dysfunction (ED). When macaque monkeys are fed a moderately atherogenic diet, they, like human beings, develop dyslipoproteinemia characterized by increased LDL-C and reduced HDL-C (Clarkson, Lab. Animal Sci. 48: 569-572, 1998; Faggiotto et al., Arterioscler. Thromb. Vasc. Biol. 4: 323-340, 1984; Faggiotto and Ross, Arterioscler. Thromb. Vasc. Biol. 4: 340-356, 1984; copies attached hereto) within 1-3 months. After consuming these diets for 5-6 months, fatty streaks develop consistently in central locations (aorta, coronary arteries) and to a lesser frequency in peripheral arteries (iliac arteries). As the atherogenic diets are continued for an additional 12 months, frequency and consistency of fatty streaks increases in the peripheral arteries, while fatty streaks progress into fibrofatty plaques in centralized locations. After consuming atherogenic diets for 4 years, fibrofatty plaques extend into the internal pudendal and penile arteries and are associated with the appearance of ED in these animals (Adams, J. Urol. 131: 571-573, 1984; copy attached hereto). Similar to human beings, Iliac artery endothelial dysfunction (measured as paradoxical constriction to acetylcholine infusion, or response to increased flow) occurs as early as three months post initiation of an atherogenic diet and precedes the development of fatty streak formation (which is not seen until 5-6 months post diet). Furthermore,

serum expression of inflammatory markers often associated with atherogenesis and impaired vascular function occurs early in the atherogenic process (Register et al., J. Clin. Endocrinol. Metab. 90: 1734-40, 2005; copy attached hereto). It should be noted that the monkeys in the seminal study by Christ et al. (2008), which documented the utility of the SMAA-Maxi-K therapy, were on such an atherogenic diet for more than 4 years. Again, for all of the aforementioned reasons it is not obvious that restricting gene transfer to a vascular smooth muscle by use of a smooth muscle-specific promotor for the treatment of a ED with a major vascular component would even be effective.

In summary, at least three concrete and independent lines of investigation "teach away" from the possibility that limiting the *hSlo* expression pattern to only the smooth muscle cells (via use of the pSMAA-*hSlo* promoter rather than the CMV-*hSlo* promoter) would provide an enhanced gene therapy approach to the treatment of erectile dysfunction.

Reconsideration and withdrawal of this rejection are respectfully requested.

Obviousness-type Double Patenting Rejections

Claims 1, 7, 20, 25, 29-30, 33, 35, and 43-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 1-3 of parent U.S. Patent No. 7,030,096 or claims 1-9 of U.S. Patent No. 6,150,338, in view of Leiden et al. (U.S. Patent No. 6,436,907) and evidenced by Foster et al. (J. Biol. Chem. 256: 11995-12003) and Melman et al. (Gene Therapy 15: 364-370, 2008).

Reconsideration and withdrawal of these rejections are respectfully requested in view of the remarks made herein above regarding the rejections under 35 U.S.C. §103(a).

CONCLUSIONS

In view of the amendments and remarks made hereinabove, reconsideration and withdrawal of the rejections in the May 4, 2011 Office Action and passage of the pending claims to allowance are respectfully requested. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

The Patent Office is authorized to withdraw the $635.00 fee for a three month extension of time for a small entity from Deposit Account No. 01-1785. No other fee is deemed necessary in connection with the filing of this reply. However, if any other fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

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